Remarks

The Office Action mailed October 13, 1006 and the Advisory Action mailed February 20, 2007 have been received and reviewed. Claims 6, 43, and 44 having been amended, claims 1-3, 5, 27, 53, and 60 having been canceled, and claims 67-71 having been added, the pending claims are claims 6-8, 10-13, 15, 17, 21, 23, 25, 28, 43-52, 54-59, and 61-71. Support for new claims 67-71 is found in canceled claim 1. Claims 60-66 being withdrawn from examination, as drawn to non-elected inventions, the claims currently under examination are 6-8, 10-13, 15, 17, 21, 23, 25, 28, 43-52, 54-59 and 67-71. Reconsideration and withdrawal of the rejections are respectfully requested.

The 35 U.S.C. §103 Rejection

Applicant acknowledges the Examiner's withdrawal of the rejection of claims 6-8, 10-13, 15, 17, 21, 23, 25, 28, 43-52, and 54-59 under 35 U.S.C. §103(a) as being unpatentable over WO 99/61040 (the '040 publication) or U.S. Patent No. 6,492,325 (the '325 patent) in view of Nykvist et al. (JBC 275(11):8255-8261, 2000), U.S. Patent No. 5,567,440 (the '440 patent) and Lin et al. (Development 128, 1573-1585 (2001)) (see page 2, Advisory Action mailed February 20, 2007).

Double Patenting Rejection

Applicant acknowledges the Examiner's withdrawal of the provisional rejection of claims 6-8, 10-13, 15, 17, 21, 23, 25, 28, 43-52, and 54-59 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 25, 34-36, 40, 43-45, and 52 of copending Application No. 10/099,573 (the '573 application) in view of Nykvist et al., U.S. Patent No. 5,567,440 and Lin et al. (see page 2, Advisory Action mailed February 20, 2007).

The 35 U.S.C. §112, Second Paragraph, Rejection

The Examiner rejected claims 28 and 48-52 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject

matter which Applicants regard as the invention. This rejection is traversed. Specifically, the Examiner asserted that the recitation "Alexa" in claims 28 and 48-52 is indefinite. Applicant submits that this rejection is overcome in view of the amendment of claims 28 and 48-52 to recite "fluorochrome."

Further, the Examiner asserted that Claims 28 and 48-52 "are indefinite because it is unclear how the referenced antibodies would inhibit binding of Alexa-conjugated purified α1β1 integrin to MCP-1 treated primary endothelial cells ***in vivo***" (page 2, Office Action mailed October 13, 2006 (emphasis added)). Claim 28 recites "wherein the antibody inhibits the binding of fluorochrome-conjugated purified α1β1 integrin to MCP-1-treated vascular endothelial cells ***in culture***" (emphasis added). Applicant respectfully submits that this recitation is describing a functional characteristic of the antibody, that the antibody inhibits binding ***in culture***, that is in vitro. Applicant submits that the metes and bound of claim 28 are clear. Likewise, claims 48-52, as amended, also recite "in culture." Applicant submits that the metes and bounds of claims 48-52 are also clear.

In view of the above discussion, reconsideration and withdrawal of the rejection of claim 28, and 48-52 under 35 U.S.C. §112, second paragraph, is requested.

The 35 U.S.C. §112, First Paragraph, New Matter Rejection

The Examiner maintained the rejection of claims 43 and 44 under 35 U.S.C. §112, first paragraph, as containing new matter (see page 2, Advisory Action mailed February 20, 2007). This rejection is traversed. Applicant acknowledges the Examiner's withdrawal of the rejection of claims 1, 3, 5, 6, 27, and 53 under 35 U.S.C. §112, first paragraph, as containing new matter.

Applicant submits that support for claim 43, amended to recite "treating a patient having chronically inflamed kidneys," is found, for example, on page 44, lines 1-8 and page 2, line 26 to page 3, line 19 of the specification. Applicant submits that claim 44, amended to recite "renal fibrosis," is fully supported by claim 11, as originally filed.

Reconsideration and withdrawal of the rejection of claims 43 and 44 under 35 U.S.C. §112, first paragraph, as containing new matter, is requested.

The 35 U.S.C. §112, First Paragraph, Enablement Rejection

The Examiner maintained the rejection of claims 6-8, 10-13, 15, 17, 21, 23, 25, 28, 43-52, and 54-59 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection is traversed.

Specifically, the Examiner asserted that "the claims are directed to a method of treating a patient having a chronic inflammatory disease associated with the interaction of Collagen XIII with α1β1 integrin monocytes . . . [but] the skilled medical practitioner would not be able to identify all the chronic inflammatory diseases or conditions associated with this interaction" (pages 2-3, Advisory Action 5, mailed February 20, 2007). Applicant respectfully disagrees. However, to expedite prosecution, claims 1-3, 5, 27, 53, and 60, all drawn to a "method of treating a patient having a chronic inflammatory disease associated with the interaction of Collagen XIII with α1β1 integrin positive monocytes," have been canceled. Applicant submits that this basis of rejection is moot in view of the cancellation of claims 1-3, 5, 6, 27, 53, and 60.

Further, the Examiner asserted that "the influence of scientific theory should depend on its empirical and demonstrable aspects and not its underlying logic" (page 2, Advisory Action, mailed February 20, 2007). Applicant respectfully requests that the Examiner identify the legal holding that substantiates this assertion. The Examiner continues with the assertion that "such empirical and demonstrable aspects of the claimed method of treating any inflammation, condition, or kidney disease with the anti-Collagen XIII antibodies are lacked [*sic*] in the instant specification" (page 2, Advisory Action, mailed February 20, 2007). Applicant respectfully reminds the Examiner that "[c]ompliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed" (MPEP 2164.02).

The Examiner further asserted that "[n]o working empirical data demonstrating theat the anti-Collagen XIII antibodies would treat or reduce any inflammation is disclosed" (page 2, Advisory Action, mailed February 20, 2007); that "the specification fails to provide

empirical data to show that [the] method would work in vivo" (page 4, Office Action mailed October 13, 2006).

In support of the methods of claims 6-8, 10-13, 15, 17, 21, 23, 25, 28, 43-45, and 54-59, Applicant provides the information in paragraphs 3 to 9 of the April 11, 2007 Declaration under 37 C.F.R. § 1.132 of Dominic Cosgrove, a copy of which is enclosed herewith.

Briefly, the shared peptide sequence of the binding site on Collage XIII for α1β1 (GAEGSPGL (SEQ ID NO:1)), as identified by phage biopanning an endothelial cell phage display library, was included in the synthesis of the larger peptide sequence GEKGAEGSPGL, which was conjugated to KLH and used as immunogen for the generation of monoclonal antibodies. Three independent hybridomas, MAB 1, MAB 2, and MAB 3, were selected based on positive ELISA binding to plates coated with the immunizing peptide. See paragraph 3 of the April 11, 2007 Declaration under 37 C.F.R. § 1.132 of Dominic Cosgrove.

Exhibit A of the April 11, 2007 Declaration under 37 C.F.R. § 1.132 of Dominic Cosgrove shows that monoclonal antibodies MAB 1, MAB 2, and MAB 3, against the binding site on collagen XIII for α1β1 integrin, neutralize adhesion of bone marrow derived monocytes to collagen XIII on embryonic fibroblasts. Cell adhesion experiments were performed using murine embryonic primary fibroblast monolayers as collagen XIII presenting cells. Fibroblasts were chosen as they had previously been shown to constitutively express collagen XIII (Hagg et al., (2001) Matrix Biol 19:727-742; Sund et al. (2001) EMBO J 20:5153-5164), avoiding the complication of having to induce collagen XIII on vascular endothelial cells. Monocytes were obtained from the bone marrow of 129 Sv mice and used directly in cell adhesion experiments. Bone marrow-derived monocytes were labeled with cell tracker dye (Molecular Probes, Eugene, OR) and layered onto confluent fibroblast monolayers in the presence or absence of either an anti-α1β1 integrin neutralizing antibody, or each of three independently derived monoclonal antibodies reactive with the peptide identified by biopanning as the binding site on collagen XIII for α1β1 integrin (MAB 1, MAB 2, MAB 3). The control antibody was an isotype matched non-reactive monoclonal, which had no effect on cell adhesion. After several washes, the total bound fluorescence was quantified. Four independent experiments were performed in triplicate and analyzed statistically (students t-test with Bonferroni correction). Asterisks indicate

significant differences in binding (p> .001). The control antibody was an isotype-matched murine monoclonal. All three of the monoclonal antibodies against collagen XIII (MAB 1, MAB 2, and MAB 3) blocked cell adhesion by approximately 80%. A neutralizing monoclonal antibody known to block α1β1 integrin binding to collagen ligands (Mendrick et al., (1995) Lab Invest 72: 367-375; Krieglstein et al., (2002) J Clin Invest 110: 1773-1782) also reduced binding of monocytes to the embryonic fibroblasts by approximately 80%. These data indicate that the α1β1 integrin-positive monocytes are binding to type XIII collagen on the embryonic fibroblasts, and that the monoclonals against the putative binding site for α1β1 integrin on collagen XIII block the interaction. See paragraph 4 of the April 11, 2007 Declaration under 37 C.F.R. § 1.132 of Dominic Cosgrove.

Exhibit B of the April 11, 2007 Declaration under 37 C.F.R. § 1.132 of Dominic Cosgrove shows that monoclonal antibodies against the binding site on collagen XIII for α1β1 integrin bind to a portion of the vascular endothelial cells in 12-week-old integrin α1-null Alport (DKO) kidneys, but not wild type littermates. MAB 2 was labeled with Alexa 568 and injected into the tail veins of wild-type or DKO mice. Twelve hours later, the kidneys were harvested and cryosections counterstained with FITC-conjugated anti-CD31 antibodies. Alexa 568 immunostaining was not observed in wild type kidney cryosections (panel A), but was abundant in DKO kidney cryosections (panel D). The vascular endothelium is immunopositive for CD31 in both wild type (Panel B) and DKO (Panel E) mice. Panel F shows some, but not all, of the vascular endothelial cells in the DKO kidneys are immunopositive for both MAB 2 and anti-CD31. Importantly, all of the Alexa 568 (MAB 2) immunostaining localizes to the vascular endothelium. Exhibit B shows that blocking antibodies against collagen XIII selectively bind the renal vascular endothelium in diseased mice, but not to that of age and strain matched controls, and bind to the endothelium in Alport kidneys under the stress of normal blood flow. See paragraph 5 of the April 11, 2007 Declaration under 37 C.F.R. § 1.132 of Dominic Cosgrove.

Exhibit C of the April 11, 2007 Declaration under 37 C.F.R. § 1.132 of Dominic Cosgrove shows that monocyte migration into the interstitial space occurs in areas where collagen XIII-positive capillaries are abundant. Sections from a twelve week old integrin

α1-null Alport mouse kidney were immunostained with either anti-collagen XIII antibody MAB 2 (Panel A), Anti-CD11b antibodies (Panel B), or both (Panel C). Panel C shows that the monocytes (in green) are abundant primarily in areas where the capillaries are immunopositive for collagen XIII (red). See paragraph 6 of the April 11, 2007 Declaration under 37 C.F.R. § 1.132 of Dominic Cosgrove.

Exhibit D of the April 11, 2007 Declaration under 37 C.F.R. § 1.132 of Dominic Cosgrove shows that treatment of Alport mice with MAB 2, a monoclonal antibody against the binding site on collagen XIII for α1β1 integrin, markedly attenuates the efflux of monocytes into the interstitium of Alport kidneys. Alport mice were given bi-weekly intravenous injections of 25 μg of MAB 2 starting at four weeks of age. Three days prior to sacrifice, mice were injected with Alexa 568-conjugated dextrans. At seven weeks of age, kidneys were harvested and cryosections either visualized directly for newly effluxed monocytes (panels A and C) or immunostained for total monocyte accumulation using anti-CD11b antibodies (panels B and D). Panels A and B show untreated Alport mice. Panels C and D show Alport mice given the MAB 2 injections. The fields shown are representative of ten independent animals. Exhibit D illustrates typical fields of transmigrated monocytes over the three-day monitoring period in Alport mice (panel A) and Alport mice treated with the monoclonal antibody MAB 2 (panel C). Comparing panel A (untreated) with panel C (treated) clearly illustrates a marked reduction in the monocyte efflux when Alport mice are given the collagen XIII blocking antibody MAB 2. This translates to a marked decrease in the total accumulation of interstitial monocytes, as indicated by anti-CD11b immunostaining (Exhibit D, compare panels B and D). Exhibit D shows that antibodies for the binding site on collagen XIII for α1β1 integrin block transmigration of α1β1 integrin positive peripheral blood monocytes into the tubulointerstitial space of Alport mice. See paragraph 7 of the April 11, 2007 Declaration under 37 C.F.R. § 1.132 of Dominic Cosgrove.

Exhibit E of the April 11, 2007 Declaration under 37 C.F.R. § 1.132 of Dominic Cosgrove shows that treatment of Alport mice with MAB 2 reduces myofibroblasts and fibrosis in the interstitium of Alport kidneys. Cryosections or either control mice (panels A and B), untreated Alport mice (panels C and D), or Alport mice treated with MAB 2 (panels E and F)

were immunostained with antibodies against either smooth muscle actin (SMA, panel A, C, and E) or fibronectin (FN, panels B, D, and F). Both myofibroblast accumulation (SMA immunostaining) and fibrosis (as determined by fibronectin immunostaining) are markedly attenuated in renal cortex of MAB 2 treated mice relative to the untreated mice. Thus, the overall reduction in interstitial monocyte accumulation shown in Exhibit D is associated with a similar reduction in myofibroblasts (Exhibit E, panels A and C), as well as fibronectin accumulation (Exhibit E, panels B and D), illustrating that administration of collagen XIII blocking antibodies results in attenuated progression of interstitial fibrosis in the Alport mouse model. See paragraph 8 April 11, 2007 Declaration under 37 C.F.R. § 1.132 of Dominic Cosgrove.

Thus, Applicant respectfully submits that one skilled in the art would conclude from the results and statements in paragraphs 3-8 of the April 11, 2007 Declaration under 37 C.F.R. § 1.132 of Dominic Cosgrove that one of skill in the art could with a reasonable expectation of success, treat a subject having an inflammatory disease or other condition where integrin α1β1-positive interstitial monocyte accumulation is observed by administering to the subject an antibody to Collagen XIII that disrupts the interaction between Collagen XIII and α1β1 integrin (claims 7, 8, 10-12, 28, 54, 61, and 67); reduce selective efflux of integrin α1β1-positive monocytes into the interstitium of chronically inflamed tissues by contacting the α1β1 integrin on peripheral blood monocytes with an antibody to Collagen XIII that interferes with the interaction between Collagen XIII and α1β1 integrin (claims 13, 15, 45, 48, 55, and 62); reduce the rate of monocyte efflux into the interstitial space of chronically inflamed tissues by contacting the tissue with an antibody to Collagen XIII wherein the antibody blocks Collagen XIII from binding with α1β1 integrin (claims 17, 21, 46, 49, 56, 63, and 69); block the interaction of α1β1 integrin on peripheral blood monocytes with Collagen XIII on vascular endothelium of chronically inflamed tissues by the monocytes, the vascular endothelium, or both with an antibody to Collagen XIII (claims 23, 25, 47, 50, 64, and 70); treat a patient having chronically inflamed kidneys associated with an accumulation of α1β1 integrin positive monocytes in the interstitium by administering to the patient an antibody to Collagen XIII, wherein the antibody reduces the rate of efflux of α1β1 integrin positive monocytes into the

renal interstitium (claims 43, 51, 58, and 65); and treat a patient having renal fibrosis by administering to the patient an antibody to Collagen XIII, wherein the antibody prevents the binding of Collagen XIII to α1β1 integrin positive monocytes (claims 44, 6, 52, 59, 66, and 71). See paragraph 9 of the April 11, 2007 Declaration under 37 C.F.R. § 1.132 of Dominic Cosgrove.

For the reasons discussed above, Applicant submits that the specification provides adequate teaching and guidance for the claimed methods. Reconsideration and withdrawal of the rejection of claims 6-8, 10-13, 15, 17, 21, 23, 25, 28, 43-45, and 54-59 under 35 U.S.C. §112, first paragraph, is respectfully requested.

Summary

It is respectfully submitted that the pending claims 6-8, 10-13, 15, 17, 21, 23, 25, 28, 43-52, 54-59, and 61-71 are in condition for allowance and notification to that effect is respectfully requested. The Examiner is invited to contact Applicant's Representatives, at the below-listed telephone number, if it is believed that prosecution of this application may be assisted thereby.

Respectfully submitted
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